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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/932,451	OZAWA ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *3,4,8,9,16,17,19,20,30,32,36 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,10-15,18,21-29,31,33-35,37,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. 8/17/01 4/29/02
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 1-40 are pending.

Election/Restrictions

Applicant's election without traverse of species VEGF and skeletal muscle in Paper filed on 1/22/03 is acknowledged.

Claim 3, 4, 8, 9, 16, 17, 19, 20, 30, 32, 36, and 38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper filed on 1/22/03.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5-7, 10-15, 18, 21-29, 31, 33-35, 37, 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for directly administering rAAV virions comprising a gene encoding an angiogenic factor to the target muscle and expressing said angiogenic factor, wherein said expression of angiogenic factor results in the formations of new blood vessels to the muscles and for increasing blood flow to the muscle, does not reasonably provide enablement for expressing said angiogenic factor wherein

said expression of said angiogenic factor results in any other therapeutic effect. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is directed to a method of delivering recombinant adeno-associated virus (rAAV) virions to a muscle comprising introducing said rAAV virions to the muscle of a mammal and expressing said angiogenic factor wherein expressing of said angiogenic factor results in a therapeutic effect. The invention lies in the field of gene therapy.

Furthermore, and with respect to claims directed to any gene therapy method and/or directed to any treatment of a mammal; the state of the art, exemplified by Anderson et al., *Nature*, Vol. 392, pp. 25-30, 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Therefore, at the time the application was filed gene therapy was considered unpredictable.

The specification provides examples that will be briefly discussed herein: The specification teaches production of a recombinant AAV-hVEGF165 vector (page 20). The specification teaches using the AAV vector in an *in vitro* rat cardiac assay (pages 21-22). The specification contemplates an in vivo ischemic heart assay using the AAV vector (page 23). The specification teaches administering an AAV-LacZ vector to rat skeletal muscle and the results displayed beta-galactosidase expression in the majority of muscle fibers (page 24). The

specification teaches administering the AAV vector to rat ischemic and contralaterlal hindlimbs (pages 24-25). The specification teaches that VEGF expression was observed 4 and 10 weeks after injection (Figure 4). The specification teaches that blood flow in AAV-VEGF165-transduced ischemic limb was increased compared to AAV-LacZ-transduced ischemic limb (page 26).

In view of the In Re Wands Factors, the claimed methods are not enabled because the breadth of the claims read on treating any disease or disorder in a patient. One skilled in the art would look to the specification for a definition for the term "therapeutic effect". The specification recites that, "be 'therapeutic effect" is meant a level of expression of one or more heterologous nucleic acid sequences sufficient to alter a component of a disease (or disorder) toward a desired outcome or endpoint, such that a patient's disease or disorder shows improvement, often reflected by the amelioration of a sign or symptom relating to the disease or disorder (page 18)." In view of the definition in the specification, the claims embrace treating any disease or disorder in a patient. There are numerous diseases that do not require an angiogenic factor, e.g., Alzheimer's Disease, OTC, muscular dystrophy, cystic fibrosis, etc. The specification lacks sufficient guidance and/or factual evidence for using an angiogenic factor to treat any disease or disorder in a patient. Furthermore, the specification lacks sufficient guidance for treating all disease or disorder in another part of a patient by administering an angiogenic factor to the skeletal muscle of a patient. For example, the specification fails to provide sufficient guidance for treating a brain, liver, kidney disease or disorder by using the claimed methods. In addition, in view of the problems with gene therapy taught by the art of record, the specification fails to teach one skilled in the art how to treat a disease or disorder that requires an

angiogenic factor that is not in the skeletal muscle. For example, the specification fails to provide sufficient guidance or evidence for treating an ischemic disorder in the eye or leg of a patient by administering the rAAV virions to the skeletal muscle of the patient. The specification teaches that after administering the AAV-VEGF165 to the hindlimb and the contralaterlal hindlimb of a rat and no VEGF expression was detected in the brain, heart, liver, spleen, kidney, and testes (page 25). The specification fails to teach one skilled in the art what dose of rAAV virions to the skeletal muscle is required to observe a therapeutic effect in another part of the body. The art of record is absent for using an angiogenic factor to treat any disease or disorder other than a disease or disorder in the skeletal muscle that requires an angiogenic factor. As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed recombinant rAAV virions generates a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any nucleic acid therapy method as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable the formations of new blood vessels to the muscles and for increasing blood flow to the muscle by directly administering to the target muscle rAAV virions and not for the full scope of the claimed invention. Given that gene therapy wherein any carrier is employed to correct a disease or a medical condition in any mammal was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any

recombinant rAAV virions cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicants' disclosure and the unpredictability of gene therapy.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 6, 10, 11, 29, 33, 34, 35, 39, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lue et al., (US 2003/0096747) taken with Colosi (US Patent 6,004,797).

Lue teaches a method of treating male erectile dysfunction or female sexual arousal disorder in a mammal comprising administering to a mammal a VEGF, BDNF, FGF, NT-3, NT-4, PDGF, Ang-1 or combination thereof via a gene therapy vector selected from the group consisting of adenovirus associated vector, retroviral vector, an adenovirus vector and a lentivirus vector (pages 4, 8, 9, and 36). Lue teaches administering via intramuscular injection to the mammal (page 36). However, Lue does not specifically teach using rAAV virions, which are free of wild-type AAV virions and helper virus.

However, at the time the invention was made, Colosi teaches adenovirus helper-free recombinant AAV virion production was routine to one of ordinary skill in the art (column 5, lines 1-3, column 40, claim 10). Colosi teaches that infectious AAV and helper virus are undesirable for several reasons, safety and health concerns and concomitant production of helper virus particles in rAAV virion producing cells diverts large amounts of cellular resources away from rAAV virion production, resulting in lower rAAV virion yields (column 3, lines 7-18). Colosi teaches that AAV has a wide host range (column 1, lines 45-46).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Lue taken with Colosi, namely to use rAAV virions, which are free of wild-type AAV virions and helper virus in the claimed methods. One of ordinary skill in the art would have been motivated to use the rAAV virions taught Colosi because rAAV virions are well known in the art for use in therapeutic methods. In addition, one

ordinary skill in the would have motivated to use the rAAV virions taught by Colosi to avoid safety and health concerns when delivering rAAV virions to an animal and concomitant production of helper virus particles in rAAV virion producing cells diverts large amounts of cellular resources away from rAAV virion production, resulting in lower rAAV virion yields.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1, 2, 5, 6, 10, 11, 12, 13, 14, 18, 21, 23, 24, 26, 28, 29, 31, 33, 34, 35, 37, 39, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al., (US 2003/0148968) taken with Colosi (US Patent 6,004,797).

Hammond teaches a method of treating a patient with a peripheral vascular disease (e.g., ischemic skeletal muscle) comprising a vector construct containing a gene encoding an angiogenic protein (pages 1, 4, 5, 8, 9, 11, 12, and 19). The vector used in the invention can be a plasmid or preferably a viral vector for example a replication deficient adenovirus or adeno-associated virus (AAV) (page 8). The vector comprising a transgene coding for angiogenic protein or peptide, such as, FGF-5, FGF-4, aFGF, and/or a VEGF (pages 8 and 9). Hammond teaches FGF members including FGF-2 (page 9). Hammond teaches that by increasing the blood flow to the affected (e.g., ischemic) region of the tissue and/or muscle (page 8). However, Hammond does not specifically teach using rAAV using rAAV virions, which are free of wild-type AAV virions and helper virus.

However, at the time the invention was made, Colosi teaches adenovirus helper-free recombinant AAV virion production was routine to one of ordinary skill in the art (column 5,

lines 1-3, column 40, claim 10). Colosi teaches that infectious AAV and helper virus are undesirable for several reasons, safety and health concerns and concomitant production of helper virus particles in rAAV virion producing cells diverts large amounts of cellular resources away from rAAV virion production, resulting in lower rAAV virion yields (column 3, lines 7-18). Colosi teaches that AAV has a wide host range (column 1, lines 45-46).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Hammond taken with Colosi to use the rAAV virions taught by Colosi to treat an ischemic condition in the mammal, wherein the rAAV virions comprises a nucleotide sequence encoding an angiogenic factor. One of ordinary skill in the art would have been motivated to use the rAAV virions taught Colosi because rAAV virions are well known in the art for use in therapeutic methods. In addition, one ordinary skill in the would have motivated to use the rAAV virions taught by Colosi to avoid safety and health concerns when delivering rAAV virions to an animal and concomitant production of helper virus particles in rAAV virion producing cells diverts large amounts of cellular resources away from rAAV virion production, resulting in lower rAAV virion yields.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1, 5, 6, and 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neufeld et al., (US 6,589,782) taken with Colosi (US Patent 6,004,797).

Neufeld teaches a method of gene therapy for cardiovascular diseases, enhancing endothelialization of diseased vessels (abstract, Figure 1, column 5 and column 20). Neufeld

teaches using adeno-associated virus in the gene therapy method (column 20). Neufeld teaches using intramuscular administration is preferred (columns 18-19 and 22). However, Neufeld does not specifically teach does not specifically teach using rAAV using rAAV virions, which are free of wild-type AAV virions and helper virus.

However, at the time the invention was made, Colosi teaches adenovirus helper-free recombinant AAV virion production was routine to one of ordinary skill in the art (column 5, lines 1-3, column 40, claim 10). Colosi teaches that infectious AAV and helper virus are undesirable for several reasons, safety and health concerns and concomitant production of helper virus particles in rAAV virion producing cells diverts large amounts of cellular resources away from rAAV virion production, resulting in lower rAAV virion yields (column 3, lines 7-18). Colosi teaches that AAV has a wide host range (column 1, lines 45-46).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Neufeld taken with Colosi to use the rAAV virions taught by Colosi to treat an ischemic condition in the mammal, wherein the rAAV virions comprises a nucleotide sequence encoding an angiogenic factor. One of ordinary skill in the art would have been motivated to use the rAAV virions taught Colosi because rAAV virions are well known in the art for use in therapeutic methods. In addition, one ordinary skill in the would have motivated to use the rAAV virions taught by Colosi to avoid safety and health concerns when delivering rAAV virions to an animal and concomitant production of helper virus particles in rAAV virion producing cells diverts large amounts of cellular resources away from rAAV virion production, resulting in lower rAAV virion yields.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1, 2, 5, 6, 7, 10, 11, 12, 13, 14, 15, 18, 21, 22, 23, 24, 29, 31, 33, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baird et al., (US 2003/0144200) taken with Colosi (US Patent 6,004,797).

Baird teaches gene delivery in vivo for treating cardiovascular diseases comprising administering a vector comprising a polynucleotide encoding VEGF (Figure 1 and pages 1, 2, 4, 5, 10-14, and 17). Baird teaches transferring to skeletal muscle (pages 13-14). Baird teaches that AAV can be used in the gene delivery method (page 13). Baird teaches that VEGF165 can be used in a method for stimulating angiogenesis in mammals (page 17). However, Baird does not specifically teach does not specifically teach using rAAV using rAAV virions, which are free of wild-type AAV virions and helper virus.

However, at the time the invention was made, Colosi teaches adenovirus helper-free recombinant AAV virion production was routine to one of ordinary skill in the art (column 5, lines 1-3, column 40, claim 10). Colosi teaches that infectious AAV and helper virus are undesirable for several reasons, safety and health concerns and concomitant production of helper virus particles in rAAV virion producing cells diverts large amounts of cellular resources away from rAAV virion production, resulting in lower rAAV virion yields (column 3, lines 7-18). Colosi teaches that AAV has a wide host range (column 1, lines 45-46).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Baird taken with Colosi to use the rAAV

virions taught by Colosi to treat an ischemic condition in the mammal, wherein the rAAV virions comprises a nucleotide sequence encoding an angiogenic factor. One of ordinary skill in the art would have been motivated to use the rAAV virions taught Colosi because rAAV virions are well known in the art for use in therapeutic methods. In addition, one ordinary skill in the would have motivated to use the rAAV virions taught by Colosi to avoid safety and health concerns when delivering rAAV virions to an animal and concomitant production of helper virus particles in rAAV virion producing cells diverts large amounts of cellular resources away from rAAV virion production, resulting in lower rAAV virion yields.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1, 5, 6, 10, 11, 12, 13, 14, 15, 21, 22, 23, 24, 25, 26, 27, 28, 29, 33, 34, 35, 39, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao (WO02/02148 A2) taken with Colosi (US Patent 6,004,797).

Gao teaches a method of promoting angiogenesis in a patient delivering to a region of tissue, such as ischemic tissue by intramuscular injection a recombinant vector comprising at least two transgenes encoding angiogenic proteins (pages 4-5 and 69 teaches using one transgene encoding a member of the FGF family (e.g., FGF-2) and a second transgene encodes a member of the VEGF family (e.g., VEGF165) (pages 5-7 and pages 21-22). Gao recites a list of various angiogenic proteins including VEGF, FGF and Angs that could be used in the method (page 7). Gao teaches using AAV vectors in the methods (pages 34-36, 40-41, 51 and 70). Gao teaches producing the viral stock ranging from 10^8 and 10^{13} viral particles (pages 42 and 48). However,

Gao does not specifically teach does not specifically teach using rAAV virions, which are free of wild-type AAV virions and helper virus.

However, at the time the invention was made, Colosi teaches adenovirus helper-free recombinant AAV virion production was routine to one of ordinary skill in the art (column 5, lines 1-3, column 40, claim 10). Colosi teaches that infectious AAV and helper virus are undesirable for several reasons, safety and health concerns and concomitant production of helper virus particles in rAAV virion producing cells diverts large amounts of cellular resources away from rAAV virion production, resulting in lower rAAV virion yields (column 3, lines 7-18). Colosi teaches that AAV has a wide host range (column 1, lines 45-46).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Gao taken with Colosi to use the rAAV virions taught by Colosi to treat an ischemic condition in the mammal, wherein the rAAV virions comprises a nucleotide sequence encoding an angiogenic factor. One of ordinary skill in the art would have been motivated to use the rAAV virions taught Colosi because rAAV virions are well known in the art for use in therapeutic methods. In addition, one ordinary skill in the would have motivated to use the rAAV virions taught by Colosi to avoid safety and health concerns when delivering rAAV virions to an animal and concomitant production of helper virus particles in rAAV virion producing cells diverts large amounts of cellular resources away from rAAV virion production, resulting in lower rAAV virion yields.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 12 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Hammond et al., (US 2003/0148968) or Baird et al., (US 2003/0144200) taken with Colosi (US Patent 6,004,797) in further view of Podsakoff et al., (IDS, US 5,858,351).

The rejection of the base claim, claim 12 under 103(a) is applied here as indicated above, by either Baird or Hammond taken with Colosi. However, either Baird or Hammond taken with Colosi do not specifically teach using about 10^6 to about 10^{15} rAAV virions to a mammal to treat an ischemic condition in the mammal.

However, at the time the invention was made, Podsakoff teaches that AAV provides efficient delivery of genes and sustained production of therapeutic proteins in various muscle cells types (column 3). Podsakoff teaches a method of expressing a gene in muscle cells in a mammal, said method comprising directly delivering to muscle cells of the mammal a recombinant AAV (rAAV) comprising a gene operably linked to control elements, wherein said gene is expressed at a level which provides a therapeutic effect in the mammal (column 25). Podsakoff teaches that the muscle cells are derived from skeletal muscle cells (column 25). Podsakoff teaches a therapeutically effective dose will be from about 10^6 to 10^{15} (column 16).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of either Baird or Hammond taken with Colosi in further view of Podsakoff to administer about 10^6 to about 10^{15} rAAV virions to a mammal to treat an ischemic condition in the mammal, wherein the rAAV virions comprises a nucleotide sequence encoding an angiogenic factor. One of ordinary skill in the art would have been motivated to use 10^6 to 10^{15} in the claimed methods because Podsakoff teaches that a therapeutically effective dose will be from about 10^6 to 10^{15}.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Conclusion

If a copy of a provisional application listed on the bottom portion of the accompanying Notice of References Cited (PTO-892) form is not included with this Office action and the PTO-892 has been annotated to indicate that the copy was not readily available, it is because the copy could not be readily obtained when the Office action was mailed. Should applicant desire a copy of such a provisional application, applicant should promptly request the copy from the Office of Public Records (OPR) in accordance with 37 CFR 1.14(a)(1)(iv), paying the required fee under 37 CFR 1.19(b)(1). If a copy is ordered from OPR, the shortened statutory period for reply to this Office action will not be reset under MPEP § 710.06 unless applicant can demonstrate a substantial delay by the Office in fulfilling the order for the copy of the provisional application. Where the applicant has been notified on the PTO-892 that a copy of the provisional application is not readily available, the provision of MPEP § 707.05(a) that a copy of the cited reference will be automatically furnished without charge does not apply.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE - Art Unit 1635, can be reached at (703) 306-3217.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER